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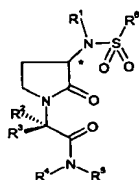
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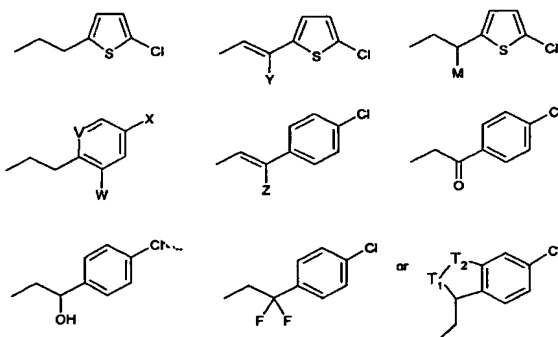
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(54) Title: PYRROLYDIN-2-ONE DERIVATIVES AS INHIBITORS OF THROMBIN AND FACTOR XA



(I)



(II)

(57) Abstract: The invention relates to compounds of formula (I), wherein : R<sup>1</sup> represents hydrogen, C<sub>1-4</sub> alkyl, -CH<sub>2</sub>CO<sub>2</sub>H, -CH<sub>2</sub>CO<sub>2</sub>C<sub>1-2</sub>alkyl, or -CH<sub>2</sub>CONR<sup>7</sup>R<sup>8</sup>; R<sup>2</sup> and R<sup>3</sup> independently represent hydrogen, -C<sub>1-6</sub>alkyl, -C<sub>1-3</sub>alkylCN, -C<sub>1-3</sub>alkylCO<sub>2</sub>H, -C<sub>1-4</sub>alkylOC<sub>1-4</sub>alkyl, -C<sub>1-4</sub>alkylS(O)<sub>n</sub>C<sub>1-4</sub>alkyl, -C<sub>1-4</sub>alkylNR<sup>10</sup>R<sup>11</sup>, -C<sub>1-3</sub>alkylNCO<sub>2</sub>C<sub>1-4</sub>alkyl, -C<sub>1-3</sub>alkylCONR<sup>7</sup>R<sup>8</sup>, -C<sub>1-3</sub>alkylCO<sub>2</sub>C<sub>0-2</sub>alkylR<sup>9</sup>, -C<sub>1-3</sub>alkylCOC<sub>0-2</sub>alkylR<sup>9</sup>, -C<sub>1-3</sub>alkylCON(R<sup>8</sup>)C<sub>0-2</sub>alkylR<sup>9</sup>, -C<sub>1-3</sub>alkylNCO<sub>2</sub>C<sub>0-2</sub>alkylR<sup>9</sup>, -C<sub>1-3</sub>alkylNCOC<sub>0-2</sub>alkylR<sup>9</sup> or -C<sub>0-2</sub>alkylR<sup>9</sup>, with the proviso that one of R<sup>2</sup> and R<sup>3</sup> is hydrogen and the other is a substituent other than hydrogen; n is an integer between 0 and 2; R<sup>4</sup> and R<sup>5</sup> together with the nitrogen atom to which they are attached form a morpholino ring; R<sup>6</sup> represents a group selected from formula (II) wherein T<sub>1</sub> and T<sub>2</sub> independently represent CH<sub>2</sub>, NH, S or O with the proviso that when one of T<sub>1</sub> or T<sub>2</sub> represents NH, S or O the other represents CH<sub>2</sub>; M represents CH<sub>3</sub>, -OH or PO; V represents CH or N; W represents H, CH<sub>3</sub>, Cl or F; X represents Cl, Br, F or -CH<sub>3</sub>; Y represents CH<sub>3</sub> or CF<sub>3</sub>; Z represents -CH<sub>3</sub> or F; R<sup>7</sup> and R<sup>8</sup> are

independently hydrogen, C<sub>1-4</sub>alkyl or together with the N atom to which they are bonded form a 5- or 6- membered non-aromatic heterocyclic ring, optionally containing an additional heteroatom selected from O, N or S; R<sup>10</sup> and R<sup>11</sup> independently represent C<sub>1-4</sub>alkyl or together with the N atom to which they are bonded form a 5- or 6- membered non-aromatic heterocyclic ring, optionally containing an additional heteroatom selected from O, N or S; R<sup>9</sup> represents phenyl or a 5- or 6- membered aromatic or non-aromatic heterocyclic group, containing at least one heteroatom selected from O, N or S, each of which is optionally substituted by 0-2 groups selected from: C<sub>1-3</sub>alkyl or halogen; and pharmaceutically acceptable derivatives thereof, processes for their preparation, pharmaceutical compositions containing them and to their use in medicine, particularly use in the amelioration of a clinical condition for which a thrombin inhibitor is indicated.



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*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*